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Gene Therapies for Sickle Cell Disease

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Exagamglogene autotemcel (Casgevy®) and lovotibeglogene autotemcel (Lyfgenia™) **may be considered medically necessary** for individuals if they meet criteria 1 through 6:

1. Are at least 2 years of age for Exagamglogene autotemcel (Casgevy®) or at least 12 years of age for lovotibeglogene autotemcel (Lyfgenia™).
2. Diagnosis of sickle cell disease.
3. Documented history of one of the following clinical signs or symptoms in the last 12 months in the setting of appropriate supportive care measures for sickle cell disease (e.g., pain management plan):
   a) Acute pain event requiring a visit to a medical facility and administration of pain medications (e.g., oral or intravenous opioids or intravenous non-steroidal anti-inflammatory drugs), hydration therapy, or red blood cell transfusions;
   b) Acute chest syndrome;
   c) Acute hepatic sequestration;
   d) Acute splenic sequestration;
   e) Priapism requiring a visit to a medical facility.
4. Meet the institutional requirements for a stem cell transplant procedure where the individual is expected to receive gene therapy (see Policy Guidelines). These requirements may include:
   a) Adequate Karnofsky performance status or Lansky performance status;
   b) Absence of advanced liver disease;
   c) Adequate diffusing capacity of the lungs for carbon monoxide (DLCO);
   d) Adequate left ventricular ejection fraction (LVEF);
   e) Absence of clinically significant active infection(s).
5. Have not received a previous allogenic hematopoietic stem cell transplant.
6. Have not received any gene therapy for sickle cell disease.

Lovotibeglogene autotemcel (Lyfgenia™) or exagamglogene autotemcel (Casgevy®) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Repeat treatment with exagamglogene autotemcel (Casgevy®) or lovotibeglogene autotemcel (Lyfgenia™) **is considered experimental, investigational and/or unproven**.

Policy Guidelines

Recommended Dose

Minimum dose is 3×10^6 $CD34^+$ cells/kg.

Dosing Limits
1 injection per lifetime.

Clinical Requirements for a Stem Cell Transplant
The requirement for eligibility for a stem cell transplant varied between the pivotal trial for exagamglogene autotemcel and lovotibeglogene autotemcel. These requirements are summarized below:

- Adequate cell counts defined as WBC < 3×10^9/L, ANC < 1×10^9/L (< 0.5×10^9/L for those on hydroxyurea treatment), or platelets < 50 to 100 × 10^9/L
- Adequate heart function defined as LVEF < 45% or cardiac T2* < 10 ms
- Advanced liver disease as defined as ALT > 3x ULN, direct bilirubin value > 2x ULN, PT INR > 1.5x ULN, history of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver biopsy
- Adequate lung function defined as DLCO < 50% of predicted value and baseline oxygen saturation < 90% without supplemental oxygen
- Adequate performance status defined as Karnofsky performance status > 60 (≥ 16 years of age) or Lansky performance status > 60 (< 16 years of age)
- Adequate kidney function as defined as eGFR < 60 to 70 mL/min/1.73 m^2
- Abbreviation Key: ALT: alanine aminotransferase, ANC: absolute neutrophil count; DLCO: lung diffusion testing; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; PT INR: prothrombin time international normalized ratio; T2: transverse relaxation time; ULN: upper limit of normal; WBC: white blood cells.

Other Considerations
There is a boxed warning for hematologic malignancy for lovotibeglogene autotemcel. Hematologic malignancy has occurred in patients treated with lovotibeglogene autotemcel. It is recommended to monitor treated individuals closely for evidence of malignancy through complete blood counts at least every 6 months for at least 15 years after treatment and through integration site analysis at months 6, 12, and as warranted.

Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. Some iron chelators are myelosuppressive. It is recommended to avoid use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after the infusion of exagamglogene autotemcel or lovotibeglogene autotemcel. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Description

Sickle Cell Disease

Sickle cell disease is a genetic disorder characterized by the presence of hemoglobin S (HbS) that includes, either from homozygosity for the sickle variant in the beta globin chain of hemoglobin (β^S/β^S) or from compound heterozygosity of a sickle beta globin mutation with another beta globin mutation (e.g., sickle-beta thalassemia such as β^S/β^0 or β^S/β^+ genotype). The homozygous from (β^S/β^S) accounts for 60% to 70% of sickle cell disease in the United States. (1)

Production of hemoglobin with dysfunctional hemoglobin S forms polymers in the red blood cells of patients. Among healthy individuals, red blood cells are flexible and round allowing them to move easily through blood vessels. With sickle cell disease, those red blood cells are sickled or shaped like crescent moons causing them to slow down or cause blockage as blood flows through the blood vessels. This results in vascular obstruction and ischemia; a shortened lifespan of the red blood cells leading to both intravascular and extravascular hemolysis, and a sticky red blood cells surface increases adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions. (2) Recurrent acute pain crises, or vaso-occlusive crises, are the most prevalent manifestations of sickle cell disease. (3) Patients also experience acute complications including serious infections and non-infectious complications such as stroke, renal necrosis, and priapism. (4) Acute chest syndrome is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms. (5) Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality. (4)

Incidence and prevalence of sickle cell disease vary considerably by geography with the highest rates in equatorial Africa, Brazil, Saudi Arabia and central India populations. (6) It is estimated that there are approximately 100,000 individuals living with sickle cell disease in the United States. (7)

As of 2008, screening for sickle cell disease in newborns is mandated in all 50 states of the United States and the District of Columbia, regardless of birth setting. (8) The diagnostic methods used after birth are those that separate hemoglobin species according to amino acid composition (hemoglobin electrophoresis or thin layer isoelectric focusing), solubility testing, and examination of the peripheral blood smear. (1)

<u>Current Treatment</u>

Specific interventions for sickle cell disease include stem cell transplantation, chronic transfusion with packed red blood cells, and hydroxyurea. While stem cell transplant can be curative, the degree of myeloablation required and lack of availability of matched donors limit its use. Chronic transfusion is generally used for primary or secondary stroke prevention. Hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises, and in those with a history of acute chest syndrome or severe anemia. (3) Hydroxyurea improves blood flow by decreasing sickling of red blood cells and altering the adhesion of red blood cells to endothelium. Also, it increases red blood cells survival and decreases white blood

cell, reticulocyte and platelet counts. (1) Acute pain crisis may be managed with pain medications including opioids and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments. (3)

In recent years, multiple specific disease-modifying treatments have been approved by the Food and Drug Administration (FDA) for treatment of complications resulting from sickle cell disease. L-glutamine supplementation is used to decrease the frequency of acute pain crises. (9) It was approved by the FDA on July 7, 2017, to reduce the acute complications of sickle cell disease in adult and pediatric individuals 5 years of age and older. Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin. (10) It was approved by the FDA on November 15, 2019, to reduce the frequency of vaso-occlusive crises in adults and pediatric individuals aged 16 years and older with sickle cell disease. It is administered intravenously in 2 loading doses 2 weeks apart and then every 4 weeks thereafter. Voxelotor is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissociation curve. (11) Voxelotor was approved by the FDA on November 25, 2019, for the treatment of sickle cell disease in adults and pediatric individuals 12 years of age and older.

Regulatory Status
On December 8, 2023, lovotibeglogene autotemcel (Lyfgenia) was approved by the FDA for the treatment of sickle cell disease in patients 12 years or older and a history of vaso-occlusive events.

On December 8, 2023, exagamglogene autotemcel (Casgevy) was approved by the FDA for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises. On January 16, 2024, the FDA expanded the approved indication to include treatment of patients aged 12 years and older with transfusion-dependent β-thalassemia.

One July 1, 2026 exagamglogene autotemcel (Casgevy) was approved by the FDA for the treatment of sickle cell disease in patients 2 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOSs) and with transfusion-dependent β-thalassemia.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials (RCTs) are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Sickle Cell Disease

Clinical Context and Therapy Purpose

The purpose of gene therapies in individuals with severe sickle cell disease is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this one-time therapy may include the following:

- Reduced complexity of one-time treatment.
- Novel mechanism of action or approach may allow successful treatment of patients for whom other available treatments have failed.
- Successful treatment may reduce the potential for disease and standard treatment-related morbidity and mortality and improve quality of life.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest are individuals with severe sickle cell disease.

Interventions

The therapy being considered is lovotibeglogene autotemcel and exagamglogene autotemcel. Both are intended to be one-time gene therapies. However, the mechanism of action is different. Lovotibeglogene autotemcel adds functional copies of a modified βA-globin gene (*βA-T87Q*-globin) into patients' hematopoietic stem cells through transduction of autologous CD34+ cells with BB305 lentiviral vector. After infusion, the transduced CD34+ hematopoietic stem cells engraft in the bone marrow and differentiate to produce red blood cells containing β^{A-T87Q} gene that will produce HbA^{T87Q} protein (functional gene therapy-derived hemoglobin). Exagamglogene autotemcel is a cellular ge ne therapy consisting of autologous CD34+ hematopoietic stem cells edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the *BCL11A* gene to reduce BCL11A expression in erythroid lineage cells. After infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells.

Comparators
The following therapies are currently being used to treat sickle cell disease. Specific interventions for sickle cell disease include stem cell transplantation, chronic transfusion with packed red blood cells, and hydroxyurea. Disease-modifying treatments approved by the FDA for treatment of complications resulting from sickle cell disease include L-glutamine, crizanlizumab and voxelotor.

Outcomes
The general outcomes of interest are change in disease status, quality of life, hospitalizations, medication use, treatment-related mortality, and treatment-related morbidity (Table 1).

Table 1. Health Outcome Measures Relevant to Sickle Cell Disease

Outcome	Detailed Outcome
Change in disease status	• Reduction in severity of clinical sequelae (acute): pain crisis, acute chest syndrome, acute myocardial infarction, stroke, kidney injury/renal infarction, splenic sequestration, priapism, reduction in hemolysis markers • Reduction in severity of clinical sequelae (chronic): pulmonary hypertension, heart failure, nephropathy/chronic kidney disease, chronic pain and fatigue
Quality of life	• Quality of life (in trials generic measures for quality of life such as Patient-Reported Outcomes Measurement Information System-57 have been used)
Hospitalizations	• Reduction in frequency or length of hospital admission • Reduction in frequency of ER visit
Medication use	• Reduction or avoidance of specific disease modifying therapy (hydroxyurea, L-glutamine, crizanlizumab and voxelotor)
Treatment-related mortality	• Mortality
Treatment-related morbidity	• Serious adverse events • Adverse events leading to treatment discontinuation

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Lovotibeglogene autotemcel

The clinical development program is summarized in Table 2. HGB-206 (referenced as Study 1-C in the prescribing label) was the basis for Food and Drug Administration (FDA) approval. While HGB-206 was initiated as a phase 1 study to evaluate the safety, preliminary efficacy, and pharmacokinetics, it was subsequently updated to a phase 1/2 registrational study to evaluate efficacy endpoints. Using learnings from the early results to optimize benefit–risk profile, the treatment process evolved over time. This led to retrospective designation of 3 sequential cohorts: Groups A, B, and C with each cohort determined by the specific treatment process used at that time. In Group A (n=7), the median peripheral blood vector copy number and HbA^{T87Q} levels were inadequate for substantial clinical effect. These improved subsequently in Group B (n=2) including improvements to cell collection and generated improved biologic and clinical efficacy including higher total hemoglobin and decreased hemolysis. Finally, Group C (n=36) demonstrated the sustained production of HbA^{T87Q} in 85% of RBCs and was the basis for FDA approval. Data from group C is reviewed in detail.

Table 2. Summary of the Clinical Development Program for Lovotibeglogene Autotemcel

Study	**Study HGB-205**	**Study HGB-206**	**Study HGB-210**	**LTF-307**
NCT Number	NCT02151526	NCT02140554	NCT04293185	NCT04628585
Phase	1/2	1/2	3	4
Study Population	Individuals ≥5 and ≤35 years of age with severe SCD or TDT regardless of the genotype	Individuals ≥12 and ≤50 years of age with SCD with either βS/βS or βS/β0 or βS/β+ genotype	Individuals ≥2 and ≤50 years of age with SCD with either βS/βS or βS/β0 or βS/β+ genotype	Individuals who enrolled in parent clinical studies (HGB-205, HGB-206 or HGB-210)
Status	Completed and published (12-14)	Completed and published (15, 16)	Ongoing	Ongoing
Study Dates	2013-2019	2020-ongoing	2021-ongoing	2020-ongoing
Design	Single arm, single-center	Single arm, multi-center	Single arm, multi-center	Long-term follow-up
Sample Size	7	45	35	85
Follow-Up	2 years	2 years	2 years	15 years

SCD: sickle cell disease; TDT: transfusion-dependent thalassemia.

Pivotal Study

Study characteristics, baseline patient characteristics, and results are summarized in Tables 3 to 5, respectively. The pivotal HGB-206 was a single-arm, 24-month, open-label, multicenter phase 1/2 study. In the study, 43 study participants underwent apheresis after mobilization with plerixafor of which 36 patients received myeloablative busulfan conditioning. Seven did not proceed to conditioning; 2 discontinued due to apheresis-related issues and 5 discontinued at

participant and/or physician discretion. Thirty-six study participants received the intravenous infusion of lovotibeglogene autotemcel. The transplant population for efficacy outcomes included patients with a history of at least 4 vaso-occlusive events (VOEs) in the 24 months prior to informed consent. The efficacy outcomes were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of lovotibeglogene autotemcel. Severe VOEs were eliminated for 94% (30/32) of evaluable patients and all VOEs were eliminated for 88% (28/32) of evaluable patients between 6- and 18-months post-infusion.

Safety data includes data from 54 study participants who initiated stem cell collection. Lovotibeglogene autotemcel was approved with a boxed warning due to potential risk of lentiviral vector-mediated insertional oncogenesis after treatment with lovotibeglogene autotemcel. Three cases of hematologic malignancy (2 cases of acute myeloid leukemia and 1 case of myelodysplastic syndrome) were reported in the pivotal trial. Two study participants who were treated with an earlier version of lovotibeglogene autotemcel using a different manufacturing process and transplant procedure (Group A) died from acute myeloid leukemia. One study participant with α-thalassemia trait (Group C) was diagnosed with myelodysplastic syndrome. The hematopoietic stress associated with mobilization, conditioning, and infusion of lovotibeglogene autotemcel, including the need to regenerate the hematopoietic system, may increase the risk of a hematologic malignancy. Patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population. As per the prescribing label, individuals treated with lovotibeglogene autotemcel should have lifelong monitoring for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment, and integration site analysis at months 6, 12, and as warranted. Other adverse reactions were related to myeloablative conditioning or underlying disease. Mobilization and apheresis triggered serious adverse events of sickle cell crisis in 6 (14%, 6/44) study participants who initiated mobilization. All study participants who initiated conditioning (100%, 45/45) experienced at least one adverse event attributed to conditioning. Most conditioning-attributed events were non-serious and were consistent with the known effects of alkylating agents. Thirty-three (73%, 33/45) study participants who received lovotibeglogene autotemcel experienced at least one serious adverse event.

The purpose of the study limitations table (Table 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time. The median (range) duration of follow-up in HGB-206 was 38 (12, 61) months. After the primary evaluation period to last follow-up, 4 of 32 patients who achieved VOE-CR experienced VOEs while maintaining globin response. After the primary evaluation period up to 24 months, 17 of 35 (49%) patients were prescribed opioids for sickle cell and non-sickle cell-related pain. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as adverse effects. Three cases of hematologic malignancies were reported. The limited sample

sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty remains about the degree of risk of insertional oncogenesis with lovotibeglogene autotemcel in real-world practice.

Table 3. Summary of Key Pivotal Trial

Study	HGB-206 (Group-C) [NCT02140554] (17)
Study Type	Single-arm, prospective
Country	United States
Dates	2020-Ongoing
Participants	**Inclusion criterion** • ≥12 and ≤50 years of age • Diagnosis of sickle cell disease with either β^S/β^S or β^S/β^0 or β^S/β^+ genotype • History of severe VOEs[a] • Failure or intolerance to hydroxyurea • Medically eligible to undergo HSCT. **Primary endpoint:** • VOE-CR[a] **Secondary endpoints:** • sVOE-CR[b] • Globin response[c]
Treatment	Lovotibeglogene autotemcel (N=36)
Follow-Up	Target: 2 years Median 38 months (range 12 to 61 months)

[a] VOEs were defined as any of the following events requiring evaluation at a medical facility: 1) an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours; 2) acute chest syndrome; 3) acute hepatic sequestration; 4) acute splenic sequestration.
[b] sVOEs were defined as either of the following events: 1) VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit; 2) priapism requiring any level of medical attention.
[c] Globin response was defined as meeting the following criteria for a continuous period of at least 6 months after drug product infusion: weighted average hemoglobin A^{T87Q} percentage of non-transfused total Hb ≥30% AND weighted average non-transfused total Hb (HbS+HbF+HbA2+HbA^{T87Q}) increase of ≥3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥10 g/dL.
CR: complete resolution; HSCT: hematopoietic stem cell transplantation; NCT: national controlled trial; sVOE: severe vaso-occlusive events; VOE: vaso-occlusive events.

Table 4. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trial

Characteristic	Transplant Population (N=36)	Transplant Population for VOE Efficacy Outcomes (N=32)
HGB-206 (Group-C) (17)		
Age, median (range), years	24 (12, 38)	25 (12, 38)
Age, n (%)		
≥18 years	28 (78%)	24 (75%)
≥12 years to <18 years	8 (22%)	8 (25%)
Male, n (%)	22 (61%)	20 (63%)
Race, n (%)		
Black	35 (97%)	31 (97%)
Not reported	1 (3%)	1 (3%)
Genotype, n (%)		
β-globin Genotype: β^S/β^S	36 (100%)	32 (100%)
α-globin Genotype: αα/αα α-globin Genotype: αα/-α3.7 α-globin Genotype[a]: -α3.7/-α3.7	23 (64%) 11 (31%) 2 (6%)	20 (63%) 10 (31%) 2 (6%)
History of Stroke[b], n (%)	5 (14%)	1 (3%)

[a] Two study participants developed anemia following treatment with lovotibeglogene autotemcel; one continues to require monthly packed red blood cell transfusions. The other has been diagnosed with myelodysplastic syndrome. Both individuals had α-thalassemia trait (-α3.7 /-α3.7).
[b] Study participants with a history of stroke were included in early inclusion criteria.

Table 5. Summary of Key Results in Pivotal Trial

Study	Results
HGB-206 (17)	
VOE-CR[a], n/N (%) [95% CI]	28/32 (88%) [71% to 97%]
sVOE-CR[b], n/N (%) [95% CI]	30/32 (94%) [79% to 99%]
Globin response[c], n/N (%)	31/36 (86%)

[a] VOEs were defined as any of the following events requiring evaluation at a medical facility: 1) an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours; 2) acute chest syndrome; 3) acute hepatic sequestration; 4) acute splenic sequestration.
[b] sVOE were defined as either of the following events: 1) VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit; 2) priapism requiring any level of medical attention.
[c] Globin response was defined as meeting the following criteria for a continuous period of at least 6 months after drug product infusion: weighted average hemoglobin A^{T87Q} percentage of non-transfused total Hb ≥30% AND weighted average non-transfused total Hb (HbS+HbF+HbA2+HbA^{T87Q}) increase of ≥3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥10 g/dL.
Note: Efficacy outcomes were complete resolution of VOE-CR and sVOE-CR between 6 months and 18 months after infusion of lovotibeglogene autotemcel.
CI: confidence interval; VOE: vaso-occlusive event.

Table 6. Study Relevance Limitations

Study	HGB-206 (17)
Population[a]	
Intervention[b]	
Comparator[c]	
Outcomes[d]	
Duration of Follow-up[e]	1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Subsection Summary: Lovotibeglogene autotemcel

In the pivotal HGB-206 (Group-C) study, a total of 36 study participants received a single intravenous infusion of lovotibeglogene autotemcel. Of the 36 total participants, 32 study participants were evaluable for the endpoints of complete resolution of VOEs and sVOEs in the 6 to 18 months post-infusion including 8 adolescent study participants. Severe VOEs were eliminated for 94% (30/32) of evaluable study participants and all VOEs were eliminated for 88% (28/32) of evaluable study participants between 6- and 18-months post-infusion. Safety data includes data from 54 study participants who initiated stem cell collection. Three cases of hematologic malignancy (2 cases of acute myeloid leukemia and 1 case of myelodysplastic syndrome) were reported in the pivotal trial. As per the prescribing label, individuals treated with lovotibeglogene autotemcel should have lifelong monitoring for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment, and integration site analysis at months 6, 12, and as warranted. Other adverse reactions were related to myeloablative conditioning or underlying disease. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period. After the primary evaluation period to last follow-up, 4 of 32 study participants who achieved VOE-CR experienced VOEs while maintaining globin response. After the primary evaluation period up to 24 months, 17 of 35 (49%) study participants were prescribed opioids for sickle cell and non-sickle cell-related pain. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most

of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty remains about the degree of risk of insertional oncogenesis with lovotibeglogene autotemcel in real-world practice.

Exagamglogene autotemcel

The clinical development program is summarized in Table 7. CLIMB-121 (referenced as Trial 1 in the prescribing label) was the basis for FDA approval and is reviewed in detail.

Table 7. Summary of the Clinical Development Program for Exagamglogene Autotemcel

NCT Number	**(Study CLIMB-121) NCT03745287**	**NCT05329649**	**NCT05477563**	**NCT05951205**	**NCT04208529**
Phase	1/2/3	3	3	3	4
Study Population	Individuals 12 to 35 years of age with severe SCD	Individuals 2 to 11 years of age with severe SCD	Individuals 12 to 35 years of age with TDT or severe SCD	Individuals 12 to 35 years of age with documented βS/βC (HbSC) genotype	Participants with β-thalassemia or sickle cell disease treated with exagamglogene autotemcel in studies NCT03655678, NCT03745287 or NCT05329649
Status	Ongoing and published (18-20)	Ongoing	Ongoing	Ongoing	Ongoing
Study Dates	2018-Ongoing	2022-Ongoing	2022-Ongoing	2023-Ongoing	2021-Ongoing
Design	Single arm, multi-center	Single arm, multi-center	Single arm, multi-center	Single arm	Observational
Sample Size	44	15	18	12	114
Follow-Up	2 years	2 years	1 year	2 years	15 years

NCT: national clinical trial; SCD: sickle cell disease; TDT: transfusion-dependent thalassemia.

Pivotal Study

Study characteristics, baseline patient characteristics and results are summarized in Tables 8 to 10, respectively. The pivotal CLIM B-121 was a single-arm, 24-month, open-label, multicenter study. (20) At the time of the interim analysis (June 2023), a total of 63 individuals enrolled in the trial, of which 58 (92%) started mobilization. A total of 44 (76%) participants received exagamglogene autotemcel infusion. Of these, 31 participants (70%) had adequate follow-up to allow evaluation of the primary efficacy endpoint and formed the primary efficacy set. The mean (SD) and median (range) number of mobilization and apheresis cycles required for the manufacture of exagamglogene autotemcel and for the back-up collection of rescue CD34+ cells were 2.3 (1.41) and 2 (1, 6), respectively. Six (10%) patients were unable to receive exagamglogene autotemcel therapy due to not achieving the minimum dose. The primary

efficacy outcome was the proportion of responders defined as participants who did not experience any protocol-defined severe vaso-occlusive crises (VOCs) for at least 12 consecutive months within the first 24 months after exagamglogene autotemcel infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was a key secondary endpoint. The primary endpoint was achieved by 29 of 31 or 93.5% participants. The key secondary endpoint of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was achieved by 100% or 30 of the 30 evaluable study participants.

Safety data includes data from 44 study participants. The adverse event profile was generally consistent with that expected from busulfan myeloablative conditioning and hematopoietic stem cell (HSC) transplant. Serious adverse reactions after myeloablative conditioning and exagamglogene autotemcel infusion were observed in 45% of patients with sickle cell disease. The most common serious adverse reactions (≥2 patients) were cholelithiasis, pneumonia, abdominal pain, constipation, pyrexia, abdominal pain (upper), non-cardiac chest pain, oropharyngeal pain, pain, and sepsis. One (2%) patient died due to a COVID-19 infection and subsequent respiratory failure. Although not observed in healthy donors and study participants, the risk of unintended, off-target editing in CD34+cells due to uncommon genetic variants cannot be ruled out.

The purpose of the study limitations tables is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period. The median (range) duration of follow-up in the pivotal trial was 19.3 months. Of the 29 study participants who met the definition of responder for the primary efficacy endpoint, one study participant experienced an acute pain episode meeting the definition of a severe VOC at month 22.8 requiring a 5-day hospitalization; this study participant was reported to have a parvovirus B19 infection at the time. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. While no cases of malignancies or unintended, off-target genome editing were reported in the trial participants, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants especially in the larger, real-world, population. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about off-target genome editing risk.

Table 8. Summary of Key Pivotal Trial

Study	CLIMB-121 (NCT03745287) (21)
Study Type	Single-arm, prospective
Country	Global

Dates	2018-Ongoing
Participants	**Inclusion** • 12 to 35 years of age • Diagnosis of sickle cell disease with ≥2 severe VOCs[a]/year in the 2 years prior to screening • Eligible for autologous HSCT • Participants aged 12 to 16 years were required to have normal transcranial Doppler **Exclusion:** • Available 10/10 human leukocyte antigen-matched related donor • Prior HSCT **Primary endpoint:** • Proportion of study participants who did not experience any protocol-defined severe VOCs[a] for at least 12 consecutive months within the first 24 months after infusion of exagamglogene autotemcel[b] **Secondary endpoints:** • Proportion of study participants free from inpatient hospitalization for severe VOCs[a] sustained for at least 12 consecutive months after infusion of exagamglogene autotemcel[b]
Treatment	Exagamglogene autotemcel (N=44)
Follow-Up	Target: 2 years Median 19.3 months (range 0.8 to 48.1 months)

[a] sVOCs were defined as an occurrence of at least 1 of the following: 1) acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or red blood cell (RBC) transfusions; 2) acute chest syndrome; 3) priapism lasting >2 hours and requiring a visit to a medical facility; 4) splenic sequestration.
[b] The evaluation started 60 days after last RBC transfusion for posttransplant support or sickle cell disease (SCD) management. The median (min, max) time to last RBC transfusion after infusion of exagamglogene autotemcel in the primary efficacy set was 19 (11, 52) days.
HSCT: hematopoietic stem-cell transplantation; NCT: national clinical trial; sVOCs: severe vaso-occlusive crises.

Table 9. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trial

Characteristic	Full Analysis Set (N=44)[a]	Primary Efficacy Set (N=31)[b]
CLIMB-121 (21)		
Age, median (range), years	20 (12, 34)	21 (12, 34)
Age, n (%)		
Adults (≥18 years and ≤35 years)	32 (73%)	24 (77%)
Adolescents (≥12 and <18 years)	12 (27%)	7 (23%)
Male, n (%)	24 (55%)	17 (55%)
Race, n (%)		
Black	38 (86%)	27 (87%)

White	3 (7%)	1 (3%)
Other	3 (7%)	3 (10%)
Genotype, n (%)		
β^S/β^S	40 (91%)	30 (97%)
β^S/β^0	3 (7%)	1 (3%)
β^S/β^+	1 (2%)	0
Annualized rate of severe VOCs in the 2 years prior to enrollment (events/year), median (range)	3.5 (2.0, 18.5)	3.5 (2.0, 18.5)
Annualized rate of hospitalizations due to severe VOCs in the 2 years prior to enrollment (events/year), median (range)	2.5 (0.5, 9.5)	2.0 (0.5, 8.5)

[a] Interim analysis conducted based on June 2023 data cut-off date.

[b] The primary efficacy set is a subset of the full analysis set. The subset was defined as all patients who had been followed for at least 16 months after exagamglogene autotemcel infusion. Patients who had less than 16 months follow-up due to death or discontinuation due to exagamglogene autotemcel - related adverse events, or continuously received red blood cell (RBC) transfusions for more than 10 months after exagamglogene autotemcel were also included in this set. An additional patient who had less than 16 months of follow-up but was otherwise determined to be a non-responder for the primary efficacy endpoint, was also included in the subset.

VOCs: vaso-occlusive crises.

Table 10. Summary of Key Results in Pivotal Trial

Study	**Results**
CLIMB-121 (21)	
Primary endpoint	
% of participants who did not experience severe VOCs[a] for ≥12 consecutive months after infusion with exagamglogene autotemcel	29/31 (94%) [98% CI: 78% to 100%]
Secondary endpoint	
% of participants free from inpatient hospitalizations for severe VOCs[a] for ≥12 consecutive months after infusion with exagamglogene autotemcel	30/30 (100%) [98% CI: 88% to 100%]
Hemoglobin concentrations	
Month 3 (n=43)	
% of total Hb comprised by HbF, mean (±SD)	36.9% (9.0)
Total Hb (mg/dL), mean (±SD)	11.9 (1.5)
Month 6 (n=38)	

% of total Hb comprised by HbF, mean (±SD)	43.9% (4.6)
Total Hb (mg/dL), mean (±SD)	12.5 (1.8)
Month 12 (n=32)	
% of total Hb comprised by HbF	43.4% (4.6)
Total Hb (mg/dL), mean (±SD)	12.5 (1.8)
Month 18 (n=27)	
% of total Hb comprised by HbF	42.3% (5.8)
Total Hb (mg/dL), mean (±SD)	13.3 (1.9)
Month 24 (n=17)	
% of total Hb comprised by HbF	42.1 (5.2)
Total Hb (mg/dL), mean (±SD)	13.1 (1.8)

[a] sVOCs were defined as an occurrence of at least 1 of the following: 1) acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusions; 2) acute chest syndrome; 3) priapism lasting >2 hours and requiring a visit to a medical facility; 4) splenic sequestration.
CI: confidence interval; Hb: hemoglobin; HbF: fetal hemoglobin; SD: standard deviation; VOC: vaso-occlusive crisis.

Table 11. Study Relevance Limitations

Study	CLIMB-121 (21)
Population[a]	
Intervention[b]	
Comparator[c]	
Outcomes[d]	
Duration of Follow-up[e]	1. Not sufficient duration for benefit 2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Subsection Summary: Exagamglogene autotemcel

In the pivotal, single-arm study CLIMB-121, a total of 44 study participants received a single intravenous infusion of exagamglogene autotemcel. Of the 44 total participants, 31 were

evaluable for the primary endpoint. The primary endpoint of proportion of study participants who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after exagamglogene autotemcel infusion was achieved by 29 of 31 or 93.5% study participants. The key secondary endpoint of proportion of study participants who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was achieved by 100% or 30 of the 30 evaluable study participants. Safety data includes 44 study participants. The adverse event profile was generally consistent with that expected from busulfan myeloablative conditioning and HSC transplant. Serious adverse reactions after myeloablative conditioning and exagamglogene autotemcel infusion were observed in 45% of study participants. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time. After the primary evaluation period to last follow-up, one of the 29 study participants who achieved primary endpoint experienced an acute pain episode meeting the definition of a severe VOC at month 22.8 requiring a 5-day hospitalization. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty remains about the degree of risk of unintended, off-target editing in CD34+cells due to uncommon genetic variants.

Summary of Evidence

For individuals with sickle cell disease who receive lovotibeglogene autotemcel, the evidence includes one single-arm prospective study. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related mortality and treatment-related morbidity. In the pivotal HGB-206 (Group-C) trial, a total of 36 participants received a single intravenous infusion of lovotibeglogene autotemcel. Of the 36 total participants, 32 were evaluable for the endpoints of complete resolution of vaso-occlusive events (VOEs) and severe VOEs (sVOEs) in the 6 to 18 months post-infusion. Severe VOEs were eliminated for 94% (30/32) and all VOEs were eliminated for 88% (28/32) of evaluable study participants between 6- and 18- months post-infusion. Safety data included 54 study participants who initiated stem cell collection. Three cases of hematologic malignancy (2 cases of acute myeloid leukemia and 1 case of myelodysplastic syndrome) were reported in the pivotal trial. As per the prescribing label, individuals treated with lovotibeglogene autotemcel should have lifelong monitoring for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment, and integration site analysis at months 6, 12, and as warranted. Other adverse reactions were related to myeloablative conditioning or underlying disease. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period. After the primary evaluation period to last follow-up, 4 of the 28 trial participants who achieved complete resolution of VOE (VOE-CR) experienced VOEs. After the primary evaluation period up to 24 months, 17 of 35 (49%) trial participants were prescribed opioids for sickle cell and non-sickle cell-related pain. Long-term follow-up (>15 years) is required to establish precision

around durability of the treatment effect as well as adverse effects. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk of insertional oncogenesis with lovotibeglogene autotemcel in real-world practice. While there is residual uncertainty around the estimates of some of the clinical outcomes, the observed magnitude of the benefit indicates that lovotibeglogene autotemcel will frequently be successful in treating sickle cell disease in at least the short-term. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with sickle cell disease who receive exagamglogene autotemcel, the evidence includes one single-arm prospective study. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related mortality, and treatment-related morbidity. In the pivotal single-arm study CLIMB-121, a total of 44 study participants received a single intravenous infusion of exagamglogene autotemcel. Of the 44 total participants, 31 were evaluable for the primary endpoint. The primary endpoint of proportion of study participants who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after exagamglogene autotemcel infusion was achieved by 29 of 31 or 93.5% study participants. The key secondary endpoint of proportion of study participants who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was achieved by 100% or 30 of the 30 evaluable study participants. Safety data includes 44 study participants. The adverse event profile was generally consistent with that expected from busulfan myeloablative conditioning and HSC transplant. Serious adverse reactions after myeloablative conditioning and exagamglogene autotemcel infusion were observed in 45% of study participants. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time. After the primary evaluation period to last follow-up, one of the 29 study participants who achieved primary endpoint experienced an acute pain episode meeting the definition of a severe VOC at month 22.8 requiring a 5-day hospitalization. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as adverse effects. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty remains about the degree of risk of unintended, off-target editing in CD34+cells due to uncommon genetic variants. While there is residual uncertainty around the estimates of some of the clinical outcomes, the observed magnitude of the benefit indicates that exagamglogene autotemcel will frequently be successful in treating sickle cell disease in at least short-term. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society of Pediatrics Hematology/Oncology Clinical Report for Health Supervision for Children and Adolescents With Sickle Cell Disease

The American Society of Pediatrics Hematology/Oncology published a clinical report in 2024. (22) The clinical report did not publish recommendations but presented an overview focused on the practical management of children and adolescents with sickle cell disease and the complications that are of particular relevance to pediatric primary care providers. This report acknowledges approval of lovotibeglogene autotemcel and exagamglogene autotemcel and states that the risks and long-term benefits of gene therapy still require investigation.

American Society of Hematology Clinical Practice Guidelines on Sickle Cell Disease

The American Society of Hematology (ASH) in partnership with the Evidence-Based Practice Research Program at Mayo Clinic published five 2019-2021 ASH clinical practice guidelines on sickle cell disease that cover sickle cell disease-related 1) cardiopulmonary and kidney disease, 2) transfusion support, 3) cerebrovascular disease, 4) acute and chronic pain, and 5) stem cell transplantation. These guidelines are available online and are updated annually. (23) Current version of the guidelines does not mention use of lovotibeglogene autotemcel or exagamglogene autotemcel. Recommendation from the 2021 guidelines for stem cell transplantation are summarized briefly. (24) The ASH guideline panel suggests:

- Human Leukocyte Antigen (HLA)-matched related HSCT rather than standard of care (hydroxyurea/transfusion) in patients with sickle cell disease who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (conditional recommendation, very low certainty in the evidence).
- Using related matched allogeneic transplantation rather than standard of care for patients with frequent pain (conditional recommendation, very low certainty in the evidence about effects).
- Using matched related allogeneic transplantation over standard of care for patients with recurrent episodes of acute coronary syndrome (conditional recommendation, very low certainty in the evidence about effects).
- Using transplants from alternative donors in the context of a clinical trial for patients with sickle cell disease with an indication for HSCT who lack a matched sibling donor (conditional recommendation, very low certainty in the evidence about effects).
- Using allogeneic transplantation at an earlier age rather than an older age in patients with an indication eligible for HSCT (conditional recommendation, low certainty in the evidence about effects).
- Use HLA-identical sibling cord blood when available (and associated with an adequate cord blood cell dose and good viability) over bone marrow (conditional recommendation, very low certainty in the evidence about effects).

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on gene therapies for sickle cell disease on August 21, 2023. The Report concluded that for people with severe sickle disease lovotibeglogene autotemcel to be incremental or better with moderate certainty of a small or substantial net health benefit (“B+”) versus standard of care and exagamglogene

autotemcel to be comparable or better with moderate certainty of a comparable or small or substantial net health benefit ("C++"). (25)

National Institute for Health and Care Excellence (NICE)

On January 31, 2025, the NICE issued the final draft of a technology appraisal guidance on exagamglogene autotemcel for treating sickle cell disease in people 12 years and over. (26) Exagamglogene autotemcel is recommended with managed access as an option for treating sickle cell disease in people 12 years and over:

- Who have recurrent vaso-occlusive crises and a β^S/β^S, β^S/β^+ or β^S/β^0 genotype, and
- When hematopoietic stem cell transplant is suitable, but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available.

It is only recommended:

- For people who have had at least 2 vaso-occlusive crises per year during the 2 previous years, and
- If the conditions in the managed access agreement for exa-cel are followed.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 12.

Table 12. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Lovotibeglogene autotemcel			
NCT04293185	A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease	35	May 2027
NCT04628585	Long-term Follow-up of Subjects With Sickle Cell Disease Treated With Ex Vivo Gene Therapy	85	Jan 2038
Exagamglogene autotemcel			
NCT05329649	Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Severe Sickle Cell Disease	13	Jun 2027
NCT05477563	Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease	26	Jun 2027
NCT04208529	A Long-term Follow-up Study in Subjects Who Received CTX001	160	Sep 2039
NCT05951205	Evaluation of Efficacy and Safety of a Single Dose of Exa-cel in Participants With Severe Sickle Cell Disease, βS/βC Genotype	12	Dec 2033 (withdrawn)

NCT05356195	A Phase 3 Study to Evaluate the Safety and Efficacy of a Single Dose of CTX001 in Pediatric Subjects With Transfusion-Dependent β-Thalassemia	15	Nov 2027

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3392, J3394

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/15/2026	Document updated. The following changes were made to Coverage: 1) Updated age criteria to state; "Are at least 2 years of age for Exagamglogene autotemcel (Casgevy®) or at least 12 years of age for lovotibeglogene autotemcel (Lyfgenia™)"; and 2) Exagamglogene autotemcel (Casgevy®) added to the experimental, investigational and/or unproven statement for all other non-Food and Drug Administration approved indications. Reference 20 added; others updated.
12/15/2025	Document updated with literature review. Medical document combined with content from RX501.166 Exagamglogene autotemcel specific to use in sickle cell disease. Additionally, the following changes were made to Coverage: 1) Revised medically necessary criteria for both exagamglogene autotemcel and lovotibeglogene autotemcel; and 2) Added "non-Food and Drug Administration approved" to the experimental, investigational and/or unproven statement. Added references 1-16 and 18-25. Title changed from "Lovotibeglogene autotemcel".
03/15/2025	Reviewed. No changes.
10/15/2024	Document updated. The following change was made to Coverage: Removed "6. Karnofsky performance status of ≥60 (≥16 years of age) or a Lansky performance status of ≥60 (<16 years of age); AND". Removed related references.
05/01/2024	New medical document. Lovotibeglogene autotemcel (Lyfgenia®) may be considered medically necessary for the treatment of individuals 12 years of age or older with sickle cell disease and a history of vaso-occlusive events when all the criteria listed in Coverage are met. Repeat treatment of Lovotibeglogene autotemcel (Lyfgenia®) is considered experimental, investigational and/or unproven. Lovotibeglogene autotemcel (Lyfgenia®) is considered experimental, investigational and/or unproven for all other indications.